

Dr Cioffi rails against our comparison of human challenge studies to organ donation, but the risk of donor death from live kidney donation is about 3 per 10,000¹ which is similar to a recent estimate of that following SARS-CoV-2 infection among people in their twenties². Lowering the age cap would reduce the risk compared to the wider age range we suggested in our paper. Furthermore, the risk to challenge volunteers may be lower if recruitment is restricted to those with no underlying health conditions. While it is likely that some small risk of severe outcomes will remain, in the absence of effective treatments, in the future it may be possible to reduce risk still further as knowledge is developed on any individual characteristics that predispose to severe outcomes.

One of our main arguments justifying human challenge trials of SARS-Cov-2 vaccines has been overlooked. Participant selection from high-transmission areas would translate into selecting from those at high background risk of natural SARS-Cov-2 infection. Moreover, in the likely over-burdened care system of a high-transmission area, access to critical care might be suboptimal, but in a challenge study it could and should be guaranteed. Thus, participation in a challenge study may not materially worsen volunteers' risk of small risk of severe disease and death.

Dr Cioffi questions the quality of consent to challenge trial participation. We agree that this aspect would need very careful attention, which may include psychiatric evaluation, but we believe that a rational person could participate in a challenge study (or donate a kidney) motivated by altruism.

Dr Cioffi's overarching allegation, that we assume a simplistic utilitarian ethic that sacrifices individual rights for collective goals, overlooks our conclusion, that human challenge trials "do not violate participants' individual rights on the altar of emergency response, but heed both individual rights and the global public health emergency." It was to show how challenge trials are consonant with participants' rights that we belabored the balance of risks and benefits to the participants, as well as their right to run their lives as sovereigns, free from paternalistic overreach.

References

1. Lentine KL, Patel A. Risks and Outcomes of Living Donation. *Adv Chronic Kidney Dis* 2012;19:220-8.
2. Verity R, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020.